Remarks/Arguments

Support for the recitation of "T" lymphocytes in the claims is in Example 74, describing the Mixed Lymphocyte Reaction (MLR) assay.

According to the Office Action, Claims 39-47 and 49-51 are pending in this application. Although the prior rejections under 35 USC 112 has been withdrawn, all claims remain rejected under 35 USC 101 for alleged lack of utility and 35 USC 112, first paragraph, and for alleged lack of enablement and written description. In addition claims 39-43, 50 and 51 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over the corresponding claims of copending application Serial No. 09/904,877.

All rejections are respectfully traversed.

Rejections under 35 USC § 101

Claims 39-47 and 49-51 were rejected as allegedly not being supported by a specific and substantial asserted utility or a well established utility. In particular, the Examiner asserts that the ability of the polypeptide to stimulate proliferation in a mixed lymphocyte reaction (MLR) is not a substantial utility "because there is no information regarding the correlation of the MLR results to any real-life diseases." According to the Examiner, "[t]here is no information regarding what subsets of immune responses, immune cell types, etc. are targeted by compounds with activities in MLRs." From this, the Examiner concludes that "there is no real-world, specific benefit to be gained from the polypeptide." Finally, the Examiner notes that the claimed protein has not been described as a member of any particular family, and hence it does not have a well-established utility.

Applicants respectfully disagree.

The mixed lymphocyte reaction (MLR) is a well-established *in vitro* assay for assessing the ability of a test compound to stimulate or suppress T cell proliferation, and consequently the immune response of an individual. The assay is described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober, National Institutes of Health, Published by John Wiley & Sons, Inc., which is referenced in Example 74, and the entire content of which expressly

incorporated by reference into the disclosure of the present application. In brief, in this method the immune response is produced by mixing T cells from antigenically distinct individuals and allowing them to react with one another in cell culture. MLR can be monitored qualitatively for example by following the incorporation of tritiated thymidine during DNA synthesis, by observing blast formation or by similar methods well known in the art.

MLR has been extensively used and is considered to be the best *in vitro* model available to study graft-versus-host disease and graft rejection. It is well known that the transplantation of tissues or organs between individuals with MHC incompatibilities quickly activates the recipient's immune system which then attempts to destroy the transplanted tissue or organ. Transplantation across minor histocompatibility loci generally induces a more indolent response. Physicians analyze the major and minor histocompatibility differences to predict the success of the graft and to adjust the aggressiveness of immunosuppressive therapy. Inhibitors of MLR find utility in suppressing unwanted immune response, which might, for example, result in graft rejection. For example, the ability of tepoxalin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated in a MLR assay (Fung-Leung *et al.*, *Transplantation* 60:362-8 (1995)). Other immunosupressants have also been routinely identified by MLR. Thus, the immunosuppressive efficacy of SNF4435 and D, produced by a strain of Streptomyces spectabilis, has been tested in MLR.

MLR has also been used to identify immunostimulators, which find utility, for example, in diseases where the T cell activation is desirable, such as various types of cancers (see, e.g. Harrison *et al.*, *Blood* 97:2764-71 (2001)), or in the case of patients whose immune system has been compromised. Thus, it has been shown that patients with AIDS-related complex demonstrate impaired autologous mixed lymphocyte reaction (Garbrecht *et al.*, *Clin. Exp. Immunol.* 67:245-51 (1987)).

PRO 335 of the present invention has been shown to stimulate T cell proliferation as measured in a MLR assay. Accordingly, inhibitors (antagonists) of PRO 335 are useful candidates for suppressing harmful immune response, e.g. in the case of graft rejection or graft versus host diseases. Similarly, the PRO 335 polypeptides or their agonists find utility in

stimulating T cell response, e.g. in the case of leukemia, and other types of cancer, and in immunocompromised patients, such as AIDS sufferers.

These utilities, which were readily understood, appreciated and accepted by those skilled in the art based on the disclosure of the present application and general knowledge in the art at its effective filing date, provide real-life, specific benefits to a large group of patients, and are believed to be sufficient to establish patentable utility for the nucleic acid molecules and related subject matter claimed in the present application.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Rejections under 35 USC § 112, first paragraph - enablement

Claims 39-47 and 49-51 were rejected under 35 USC 112, first paragraph, since in lack of a specific and substantial asserted utility or a well-established utility, one skilled in the art clearly would not known how to use the claimed invention.

In response to the previous rejection, Applicants have shown that the claimed invention is supported by a specific and substantial asserted utility, the present rejection should be withdrawn.

Rejections under 35 USC § 112, first paragraph -enablement and written description

Claims 39-47 and 49-51 were rejected as allegedly lacking enablement and written description for variants of the disclosed sequence. According to the rejection, Applicants' amendment incorporating a functional limitation is not sufficient to overcome this rejection, "because the functional limitation is not considered to be a definite use of the polypeptide for the reasons set forth above."

In response to the lack of utility rejection, applicants have shown that the immunostimulatory activity is a specific utility. Accordingly, its recitation in the claims is a specific functional limitation. In addition, the claims have been amended to specifically state that the proliferation of stimulated T lymphocytes is stimulated. Since the genera of the rejected claims are characterized by a combination of well defined structural and functional limitations, the Examiner is respectfully requested reconsider the present rejection.

Provisional obviousness-type double patenting rejection

Claims 39-43, 50 and 51 have been rejected under the judicially created doctrine of obviousness-type double patenting over the corresponding claims of copending Application No. 09/904,877. The attached Terminal Disclaimer is believed to overcome this rejection, the withdrawal of which is respectfully requested.

All claims pending in this application are believed to be in prima facie condition for allowance, and an early action to that effect is respectfully solicited.

Please any additional fees, including any additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C46). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 7, 2003

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